REMARKS

The Amendments

In the Specification

Applicant has amended the specification at various places to correct minor typographical, grammatical, and graphical errors. In particular, applicant has amended the specification at pages 3, 4, 6, 10, 11, 21, 30-36, 41, 44, 46, and 47 by adding a hydrogen atom to nitrogen, carbon, or oxygen atoms previously depicted with incorrect valences. These inadvertent typographical and graphical errors would have been obvious to one of ordinary skill in the art because nitrogen is trivalent, carbon is tetravalent, and oxygen is bivalent. Applicant has amended the specification at pages 2, 8, 23, 52, 53, 57, 81, and 86 to correct obvious typographical and grammatical errors.

Applicant has also amended the specification at pages 5 and 8 to delete each occurrence of "C_1-C_3 alkenyl" and to recite therefor "C_2-C_3 alkenyl". One of skill in the art would recognize that C_1-alkenyl is not chemically feasible.

Applicant has deleted a redundant "-OCH_3" group from the list of Q_2 substituents at page 11.

Applicant has corrected the chemical structure of compound 34 at page 19, in which the nitro group was incorrectly depicted as "N(O)-OH". One of skill in the art would recognize this obvious and inadvertent error.

Applicant has amended the specification to delete the phrase "(which is depicted in Table 1)" at page 65.

Applicant has amended the specification at page 106 to correct inadvertent typographic errors in the definition of the symbols used in Table 7, wherein the characters ">" and "<" were transposed. In particular, applicants have amended page 106, lines 2 and 5, to recite that the symbol "+++" represents IC_{50} values "<0.1 μM"; page 106, line 4, to recite that the symbol "+" represents IC_{50} values ">1.0 μM"; page 106, lines 6 and 9, to recite that the symbol "+" represents IC_{50} values ">0.5 μM"; and page 106, line 7, to recite that the symbol "+++" represents IC_{50} values "<0.25 μM". These typographic errors would have been obvious to one of skill in the art because in Table 7, compounds with IC_{50} values of "+++" are better inhibitors than compounds with IC_{50} values of "+", and it is well known in the art that compounds with lower numerical IC_{50} values are better inhibitors than compounds with higher numerical IC_{50} values. Applicant's amendments correct these inadvertent errors.

In the Claims

Claims 3, 8-15, 18-23, and 25-37 are pending in the application. Claims 1-2, 4-7, 16-17, and 24 were previously canceled. The Examiner has withdrawn claim 13 from further consideration pursuant to 37 C.F.R. § 1.142(b). Applicants have canceled claims 13-14, 30-33, and 35-37 and have amended claims 3, 10, 11, 26-29, and 34, as indicated below. The cancellation of this and any other subject matter is without waiver of applicants' rights to file divisional or continuing applications directed to this subject matter and claiming priority to this application under 35 U.S.C. § 120.

In particular, applicants have amended claim 3 and have canceled claims 13 and 14 to be consistent with the subject matter elected for further prosecution in their June 23, 2005 Reply to Restriction Requirement ("the June 23, 2005 Reply").

Applicants have also amended the definition of "R^{2}" in claim 3 by replacing "$(C_1$-$C_3)$-alkenyl" with "$(C_2$-$C_3)$-alkenyl". One of skill in the art would recognize that C_1-alkenyl is not chemically feasible.

Applicants have amended claim 10 to correct minor spelling errors.

Applicants have amended claim 11 to correct a typographical error in "$-C(R^2)_2-$". Support for this amendment appears, e.g., at specification page 7, and in claim 1, as originally filed.

Applicants have amended claims 27-29 and 34 to clarify the antecedent basis for the term "method".

Applicants have amended claims 3, 26-29, and 34, as discussed below, in response to the Office Action. These amendments are supported throughout the specification. See, e.g., original claims 3, 26, 28, and 34.

None of the amendments adds new matter. Their entry is requested.

The Restriction Requirement

Applicants confirm the election of Group I, claims 3, 8-12, 14-15, 18-23, and 25-37, drawn to pyridine compounds of formula Ie or Ig, in their June 23, 2005 Reply.

The Rejections

35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 26-37 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of treating rheumatoid arthritis, allegedly does not provide enablement for a method of treating all other diseases or preventing the diseases of the instant claims. According to the Examiner, "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims." Office Action, page 3. Applicants traverse.

Applicants disagree that the instant specification does not fully enable methods of claims 26-37. Solely to expedite prosecution, however, applicants have canceled claims 30-33 and 35-37 and have amended claims 26-29 and 34. As amended, claims 26-29 and 34 are directed to preferred methods of treatment. Applicants respectfully submit that amended claims 26-29 and 34 are fully enabled for at least the following reasons.

Applicants have described in the specification numerous *in vitro* assays for determining that the compounds of the present invention are inhibitors of p38. See, e.g., specification page 52. Having read the specification, one of skill in the art would readily be able to test the present compounds for their ability to inhibit p38. Based on the p38 inhibitory activity, that skilled artisan would know that the present compounds are useful against the claimed diseases, as discussed below.

Contrary to the Examiners contention, p38 has been implicated in a broad array of disease states and target organs. See, e.g., specification page 2, lines 10-23, and page 53, line 8, to page 56, line 20. Each of the diseases recited in amended claims 26-29 and 34 is mediated by cytokines and other inflammatory proteins that are in turn mediated by p38. Inhibiting p38 kinase leads to a blockade of the production of IL-1 and TNF. IL-1 and TNF, in turn, stimulate the production of cytokines such as IL-6 and IL-8. See, e.g., specification page 2, lines 3-9. Thus, inhibiting p38 would lead to a blockade of production of IL-1, TNF, IL-6 and IL-8 and other pro-inflammatory proteins. IL-1, TNF, IL-6, and IL-8 are all involved in various inflammatory and immune responses. Thus, the diversity of actions of p38 kinase gives rise to a broad range of applications for the p38 inhibitors of the present invention.

In support of the link between p38 and the claimed diseases, applicant submits herewith nine journal articles. These articles confirm the link between p38 and rheumatoid arthritis, endotoxin-induced shock, Crohn's disease, burn-mediated cardiac dysfunction, cardiac hypertrophy, congestive heart failure, pulmonary inflammation, and ischemia.[1]

More specifically, Suzuki has confirmed a link between p38 and the inflammatory cytokines IL-6 and IL-8.[2] Suzuki showed that treatment of rheumatoid synovial

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[1] Some of the documents submitted herewith were published after the filing date of the present application and as such, evidence the level of ordinary skill in the art at the time of filing. *See* M.P.E.P. § 2124 and *Gould* v. *Quigg*, 822 F.2d 1074, 1077 (Fed. Cir. 1987) (a later-dated publication may be offered "as evidence of the level of ordinary skill in the art at the time of the application and as evidence that the disclosed device would have been operative").

[2] Suzuki, M. et al., "The Role of p38 Mitogen-Activated Protein Kinase in IL-6 and IL-8 Production from the TNF-α- or IL-1β-stimulated Rheumatoid Synovial Fibroblasts," FEBS Letters, 465, pp. 23-27 (2000) ("Suzuki", Exhibit 1).

fibroblasts with a p38 inhibitor led to specific suppression of IL-6 and IL-8 production, thereby demonstrating that "p38 MAP kinase is involved in the induction of inflammatory cytokines" (Suzuki, p. 26). Accordingly, p38 inhibitors may be effective for the treatment of rheumatoid arthritis and other inflammatory and autoimmune diseases in which inflammatory cytokines play a crucial role.

Badger I also demonstrates that inhibition of p38 inhibits production of inflammatory cytokines.[3] Specifically, Badger I supports a correlation between inhibition of p38 and inhibition of the pro-inflammatory protein TNF-α (Badger I, p. 1455). Badger I reports the efficacy of a p38 inhibitor in a variety of TNF-α-mediated animal models of inflammatory diseases that arise by both autoimmune and infectious pathways. Administration of a p38 inhibitor reduced joint edema by 72 and 45% in the mouse collagen-induced arthritis model; reduced paw inflammation in the rat adjuvant arthritis model; inhibited bone resorption in the fetal rat long bone assay; and improved mouse survival in a model of endotoxin-induced shock (Badger I, p. 1459-60).

Badger II further supports the link between p38 and inflammatory cytokine synthesis.[4] As discussed in Badger II, "inhibition of p38 MAP kinase and subsequent

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[3] Badger, A.M. et al., "Pharmacological Profile of SB 203580, a Selective Inhibitor of Cytokine Suppressive Binding Protein/p38 Kinase, in Animal Models of Arthritis, Bone Resorption, Endotoxin Shock and Immune Function," J. Pharmacol. Exp. Ther., 279, pp. 1453-1461 (1996) ("Badger I", Exhibit 2).

[4] Badger, A.M. et al., "Disease-Modifying Activity of SB 242235, a Selective Inhibitor of p38 Mitogen-Activated Protein Kinase, in Rat Adjuvant-Induced Arthritis," Arthritis Rheum., 43, pp. 175-183 (2000) ("Badger II", Exhibit 3).

inhibition of the synthesis of a number of important proinflammatory proteins has been identified as the primary mechanism contributing to the antiinflammatory activity of [p38 inhibitors]" (Badger II, p. 181). Importantly, the p38 pathway is "commonly associated with the early stages of host response to injury and infection" (Badger II, p. 181). Badger II observed significant antiinflammatory activity in an aggressive arthritis model of Lewis rats treated either prophylactically or therapeutically with a p38 inhibitor. Rats treated at 60 mg/kg showed 73% inhibition of paw edema and 53% normalization of bone mineral density (Badger II, p. 182). A p38 inhibitor has thus been demonstrated to have antiinflammatory effects and to protect against bone damage (Badger II, p. 182).

Humans with Crohn's Disease ("CD") have responded favorably to treatment with a p38 inhibitor in a clinical trial reported by Hommes.[5] CD is a chronic inflammatory disease that arises via an autoimmune response (Hommes, p. 7). Hommes treated 12 patients suffering from moderate to severe CD with a p38 inhibitor and reported a corresponding decrease in TNF-α production in addition to significant clinical effects (Hommes, p. 13). Thus, a correlation between p38 inhibition and the treatment of inflammatory and autoimmune diseases, including CD, has been demonstrated.

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[5] Hommes, D. et al., "Inhibition of Stress-Activated MAP Kinases Induces Clinical Improvement in Moderate to Severe Crohn's Disease," Gastroenterology, 122, pp. 7-14 (2002) ("Hommes", Exhibit 4).

Ballard-Croft further supports the finding that p38 acts through the activation of inflammatory cytokines such as TNF-α.[6] Specifically, Ballard-Croft has linked p38 inhibition to the inhibition of cardiomyocyte secretion of TNF-α and the prevention of burn-mediated cardiac dysfunction (Ballard-Croft, p. H1978). These findings indicate that administration of a p38 inhibitor interrupts postburn inflammation by targeting cardiac myocytes (Ballard-Croft, p. H1978).

Shimamoto has confirmed a correlation between p38, IL-1 and cardiac hypertrophy and congestive heart failure.[7] As discussed in Shimamoto, treatment of Dahl salt-sensitive rats with a p38 inhibitor "suppressed IL-1β production" and "prevented progression of cardiac hypertrophy and congestive heart failure" (Shimamoto, p. 1415).

The anti-inflammatory effects of p38 have also been shown to occur in the absence of generalized immunosupression, where, for example, p38 exerts an effect on inflammatory cytokines via a signal transduction pathway. Nick[8] showed that administration of a p38 inhibitor modulated neutrophil influx in pulmonary inflammation (Nick, p. 2159).

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6 Ballard-Croft, C. et al., "Role of p38 Mitogen-Activated Protein Kinase in Cardiac Myocyte Secretion of the Inflammatory Cytokine TNF-α," Am. J. Physiol. Heart Circ. Physiol., 280, pp. H1970-H1981 (2001) ("Ballard-Croft", Exhibit 5).

7 Shimamoto, A. et al., "Inhibition of p38 Mitogen-Activated Protein Kinase Suppresses Interleukin-1β-Expression and Prevents Progression of Cardiac Hypertrophy and Congestive Heart Failure in Rats," American Heart Association Annual Meeting (2000) ("Shimamoto", Exhibit 6).

8 Nick, J.A. et al., "Role of p38 Mitogen-Activated Protein Kinase in a Murine Model of Pulmonary Inflammation," J. Immunol., 164, pp. 2151-2159 (2000) ("Nick", Exhibit 7).

Specifically, inhibition of p38 in a murine model of LPS-induced lung inflammation resulted in a loss of neutrophil migration due to a reduced neutrophil chemotaxic response (Nick, p. 2158).

p38 may also attenuate this signaling cascade in addition to its inflammatory effects. Legos has shown a p38 inhibitor to exhibit a neuroprotective effect through direct effects on ischemic brain cells.[9] p38 is present in the brain "in a wide variety of cell types including neurons, astrocytes, endothelial cells and leukocytes" (Legos, p. 74). p38 activation in the brain is an early response to the cellular stresses of severe focal ischemia, focal stroke, and myocardial/ischemia reperfusion injury (Legos, p. 75). Legos demonstrates that spontaneously hypertensive rats treated with 15 mg/kg of a p38 inhibitor 1 hour pre- and 6 hours post-middle cerebral artery occlusion showed significant neuroprotection, including behavioral improvements and a 48% reduction in infarct volume (Legos, p. 73). Thus, Legos supports a correlation between p38 and neurodegenerative diseases.

Barancik further supports the finding that inhibition of p38 protects against ischemic injury.[10] As discussed in Barancik, "p38-MAPK is part of a pathway accelerating cell death" (Barancik, pp. 481-482). Administration of a p38-specific inhibitor before and during myocardial ischemia protected pig myocardium against ischemic cell death (Barancik, p. 480).

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[9] Legos, J.J. et al., "SB 239063, a Novel p38 Inhibitor, Attenuates Early Neuronal Injury Following Ischemia," Brain Research, 892, pp. 70-77 (2001) ("Legos", Exhibit 8).

[10] Barancik, M. et al., "Inhibition of the Cardiac p38-MAPK Pathway by SB203580 Delays Ischemic Cell Death," J. Cardiovasc. Pharmacol., 35, pp. 474-484 (2000) ("Barancik", Exhibit 9).

Therefore, Barancik further supports the action of p38 via a signaling cascade rather than through inflammatory effects.

In sum, the documents of record have established a link between p38 and various disease states via diverse mechanisms. They also demonstrate that p38 inhibition has in vivo effects in animals, including humans, against the diseases recited in amended claims 26-29 and 34.

In view of the teachings of the specification and the knowledge in the art at the time this application was filed, the skilled artisan would be able to practice the claimed methods without undue experimentation and would expect that the claimed methods have the asserted utility. Accordingly, the claimed methods pass muster of Section 112, first paragraph.

35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 3, 8-12, 14-15, 18-23, and 25-37 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner asserts that the terms "-$S(O_2)$-" and "-$N(R_2)$-" in the claim 3 definition of "X" are repeated. Office Action, page 9. Applicants have obviated the rejection by amending claim 3 to delete the repeated terms. Applicants respectfully request that the rejection be withdrawn.

Double patenting

The Examiner has rejected claims 3, 8-12, 14-15, 18-23, and 25 under the judicially created doctrine of obviousness-type double patenting as allegedly being

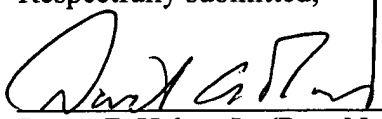
unpatentable over claims 1-14 of U.S. Patent No. 6,632,945. Office Action, page 10. According to the Examiner, although the claims are not identical, they are not patentably distinct from each other because the instant claims allegedly substantially overlap the compounds of the reference claims. Applicants traverse.

Applicants disagree that the rejected claims are not patentably distinct from claims 1-14 of U.S. Patent No. 6,632,945. Applicants will, however, consider filing a terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) upon notice that the claims are otherwise in condition for allowance.

Conclusion

In view of the above, applicants request that the Examiner enter the above amendments, consider the accompanying arguments, withdraw the rejections, and allow the pending claims to pass to issue.

Respectfully submitted,



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